Stereoselective Ethynylation and Propargylation of Chiral Non-racemic Cyclic Nitrones. Application to the Synthesis of Glycomimetics

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Abstract

Ethynylation and propargylation of chiral non-racemic polyhydroxylated cyclic nitrones with Grignard reagents are efficient methods for preparing building blocks containing an alkyne moiety to be used in copper catalyzed azide alkyne cycloaddition click-chemistry. Whereas ethynylation takes place with excellent diastereoselectivity, propargylation afforded mixtures of diastereomers in some cases. The use of trimethylsilyl propargyl bromide as precursor of the Grignard reagent was necessary to avoid the formation of undesired allene derivatives. DFT calculations explain, within the experimental error, the observed behavior. Condensation of the obtained pyrrolidinyl alkynes with sugar azides derived of β-(1,3)-glucans provides glycomimetics suitable to be used against fungal transglycosylases

Keywords

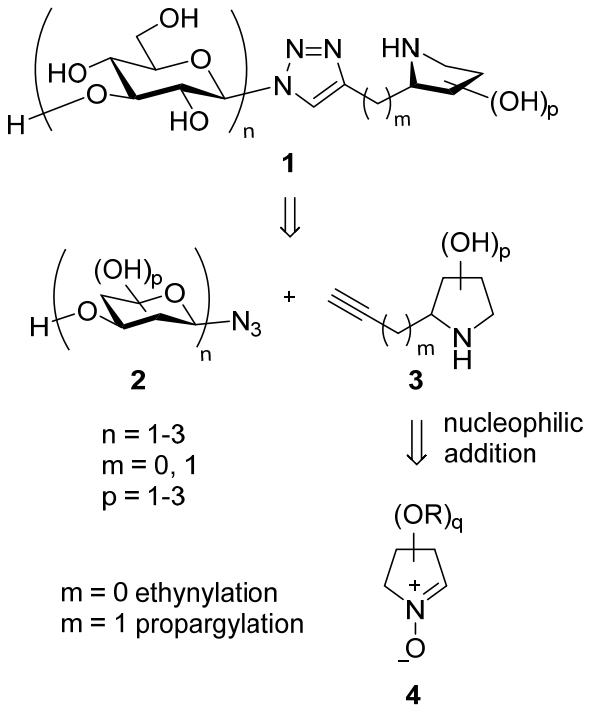
Nitrones; Ethynylation; Propargylation; Alkynes; Click-Chemistry; Glycomimetics

Introduction

Scleroglucan is a polymer that forms the fungal cell wall which consists of a linear β-(1,3)-D-glucose backbone with one β-(1,6)-D-glucose side chain every three main residue cross-linked with quitin through a unit of *N*-Ac glucosamine.[1] Inhibition of its synthesis caused fungal death and thus enzymes involved in the synthesis and metabolism of scleroglucan are potential targets for developing new antifungal drugs.[2] The development of suitable enzymatic inhibitors of carbohydrate-active enzymes requires depth knowledge of the mode of action of the target enzyme.[3] In this context,

tailor-made glycomimetics are of great utility for understanding carbohydrate-protein interactions. [4] Also, it is well-know that polyhydroxylated pyrrolidines (iminosugars) are excellent surrogates of carbohydrates mimicking the transition state of several enzymes, mainly glycosyl hydrolases.[5]

In a research project focused on the design of polyhydroxylated pyrrolidinyl-derived glycomimetics **1** incorporating β-(1,3)-D-glucose units targeting fungal transglycosylases,[6] we envisaged that the triazole ring, easily accessible through well-known click-chemistry[7] and extensively used in glycobiology,[8] would be a suitable linker between the nitrogenated heterocycle and the carbohydrate unit. According to the retrosynthetic approach shown in Scheme 1 where the corresponding carbohydrate azide **2** is easily accessible, it is necessary to develop an efficient methodology for introducing the required triple bond into the pyrrolidine ring providing key intermediates **3**. A well-established synthetic route to 2-substituted polyhydroxylated pyrrolidines consists of a nucleophilic addition to the corresponding cyclic nitrone **4**.



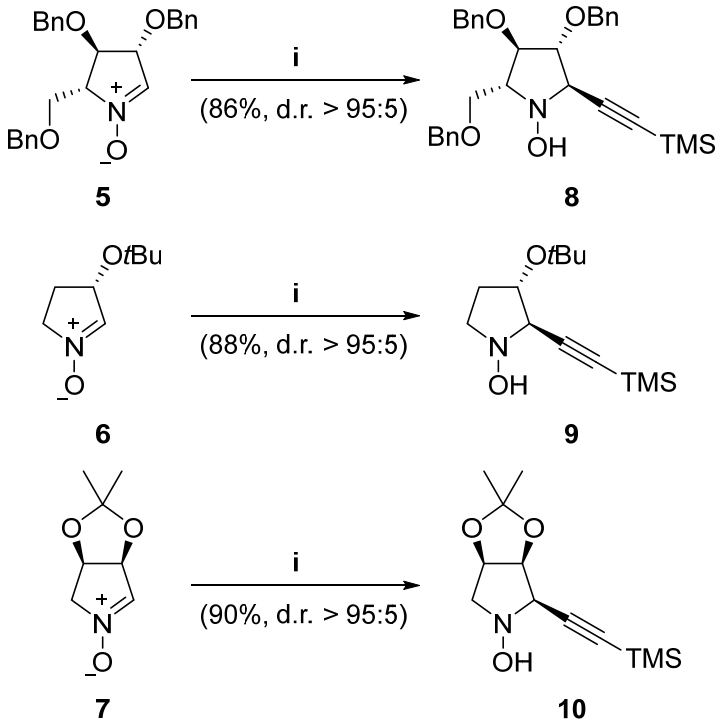
Scheme 1. Retrosynthetic analysis for glycomimetics **1**

We and others have reported a variety of nucleophilic additions to **4**,[9] including allylation,[10] alkylation[11] and hydrocyanation[10c, 12] reactions, and in all cases excellent yields and stereoselectivities were obtained. On the other hand, few particular cases have been reported on the direct ethynylation of cyclic nitrones[13] in comparison with the

same reaction on acyclic nitrones.[14] Similarly, propargylation of nitrones has also been scarcely explored and only one example has been described.[13d] In this paper, we report a novel and stereoselective synthesis of alkynyl and propargyl pyrrolidines **3** from nitrones **4** and demonstrate their utility in the construction of glycomimetics **1**.

Results and Discussion

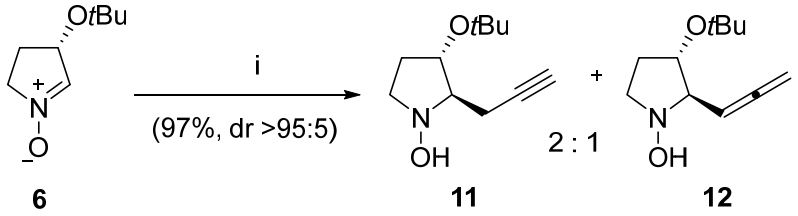
The starting nitrones **5-7** used for this study were prepared from D-arabinose for nitrones **5** [15] and **7**,[16] and from L-malic acid for nitrone **6**.[17] The ethynylation reaction was carried out following our previousy reported protocol for acyclic nitrones[18] using lithium trimethylsily acetylide generated *in situ* at -80ºC (Scheme 2). In all cases the reaction proceeded smoothly in 20 min in good yield and excellent diastereoselectivity, only one diastereomer being detected by NMR. The configuration of the newly created stereogenic center at C-2 was determined to be *trans* with respect to C-3 of the pyrrolidine ring by NMR spectroscopy (NOESY 2D experiments).



Scheme 2. Trimethylsilyl ethynylation of cyclic nitrones. Reagents and conditions: (i) trimethylsilyl acetylene (2.5 eq), BuLi (2.5 eq), THF, -80ºC, 20 min.

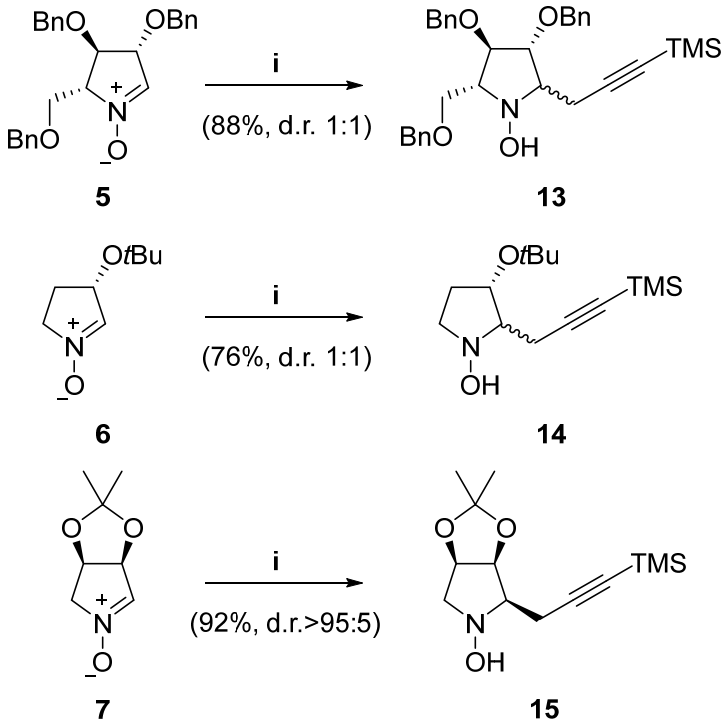
Propargylation of nitrones **5**-**7** was trickier than ethynylation. A first attempt consisting of the reaction between nitrone **6** and allenylylmagnesium bromide formed *in situ* from propargyl bromide and Mg in the presence of mercury(II) chloride,[19] afforded, in a

complete diastereoselective way and excellent yield, a 2:1 mixture of the expected product **11** and the corresponding undesired allene **12** (Scheme 3). In fact, the obtention of the allenyl derivative had been extensively reported in propargylation of imines.[20]



Scheme 3. Direct propargylation of **6**. Reagents and conditions: (i) propargyl bromide (3.0 eq), Mg, $HgCl_2$, THF, 0 ºC, 20 min.

On the other hand, it has been reported that propargylation with the Grignard reagent derived from trimethylsilylpropargyl bromide afforded the propargyl derivative almost exclusively in most cases.[21] We carried out the reaction of nitrones **5**-**7** with trimethylsilylpropargylmagnesium bromide,[22] formed *in situ* from trimethylsilyl propargyl bromide and Mg in the presence of mercury(II) chloride,[23] and the corresponding propargyl derivative was obtained as the only product of the reaction. Surprisingly, in the case of nitrones **5** and **6** a complete lack of selectivity was observed and 1:1 mixtures of inseparable hydroxylamines **13** and **14** were obtained, respectively. Attempts by carrying out the reaction in the presence of Lewis acids, that had shown to be useful for modulating stereoselectivity in nucleophilic additions to nitrones,[24] were unsuccessful. Only nitrone **7** afforded enantiomerically pure **15** as the only product of the reaction (Scheme 4). The configuration of the newly created stereogenic center at C-2 was determined to be *trans* with respect to C-3 of the pyrrolidine ring in compound **15** by NMR spectroscopy (NOESY 2D experiments). In the case of hydroxylamines **13** and **14** complete identification of the compounds was achieved by selective TOCSY experiments.



Scheme 4. Trymethylsilyl propargylation of cyclic nitrones. Reagents and conditions: (i) trimethylsilyl propargyl bromide (3.0 eq), Mg, $HgCl_2$, THF, 0 ºC, 20 min.

For a rationalization of the observed results in both ethynylation and propargylation, DFT calculations at M06-2X/6-311+G(d,p)//M06-2X/6-31G(d,p) level of theory considering solvent effects (PCM model; THF or diethylether depending on the reaction studied).[25] The ethynylation reaction can be explained by a typical sterical model, similar to that observed in the vivnylation of cyclic nitrones,[24a] in which the nucleophile attacks preferentially by the less-hindered face. Figure 1 illustrates the transition states corresponding to nitrone **6** for which the difference of 3.0 kcal/mol in favour of *Re*-**TSA1** predicted a *trans:cis* ratio in good agreement with the experimental observations.

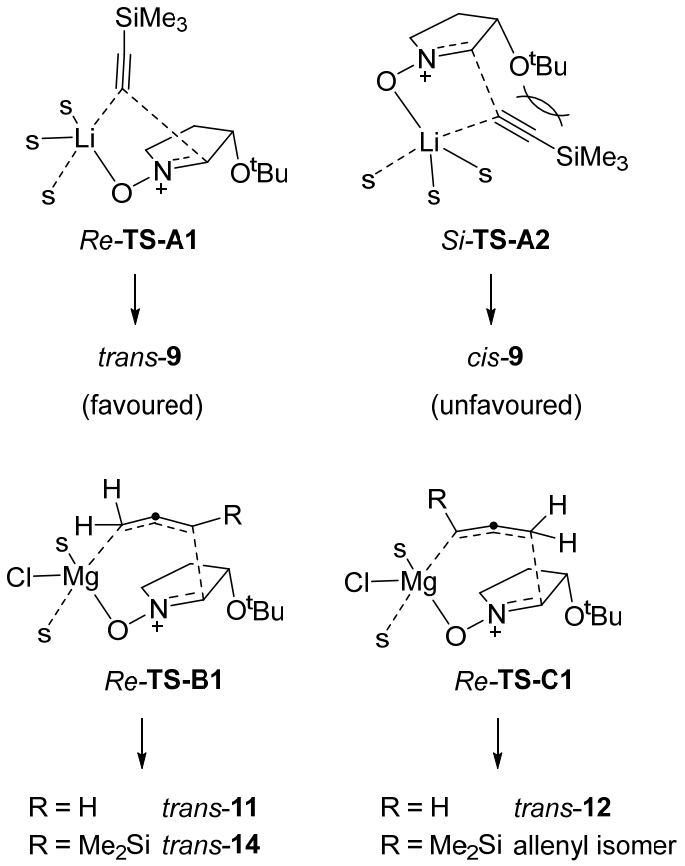
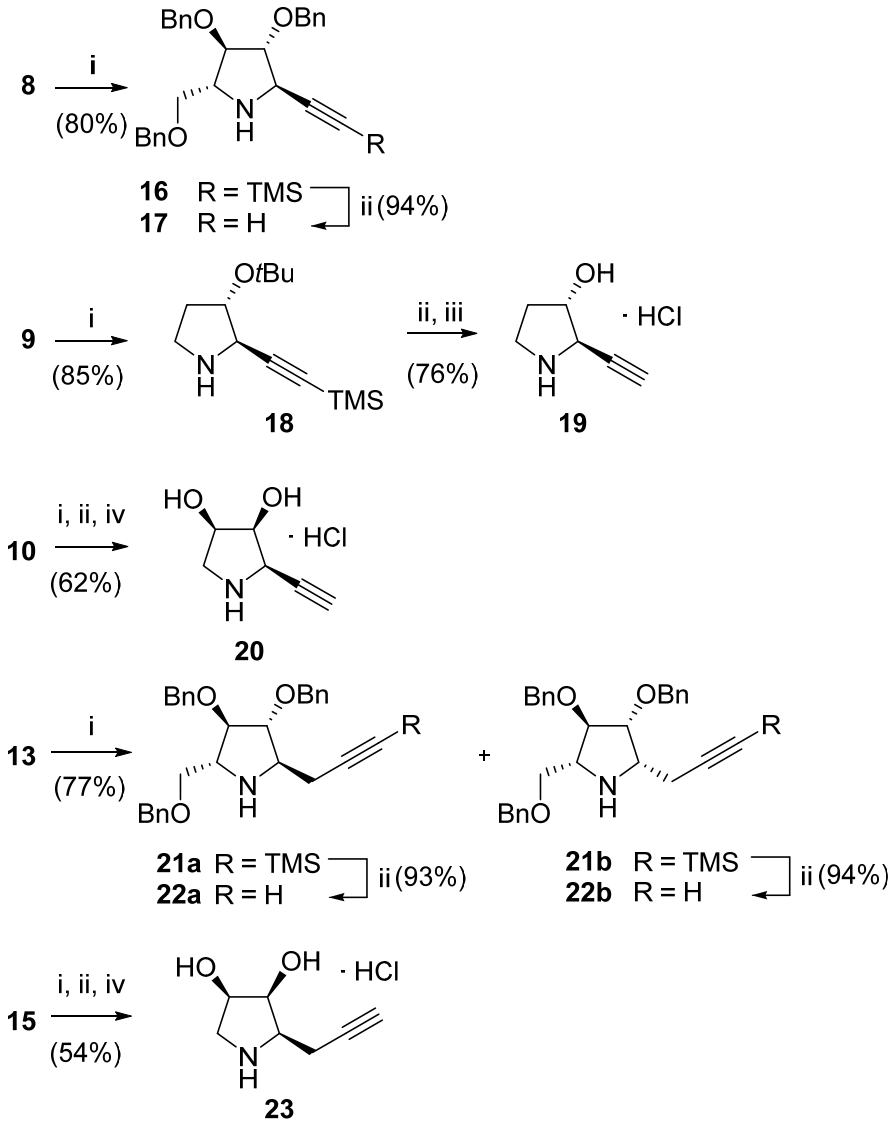


Figure 1. Preferred transition state for the ethynylation (*Re*-**TS-A1** and *Si*-**TS-A2**) and propargylation (*Re*-**TS-B1** and *Re*-**TS-C1**) of cyclic nitrones. Relative free energies are given in kcal/mol

The mechanism of propargylation of cyclic nitrones should consider the metallotropic equilibrium between allenyl- and propargylmagnesium bromide,[26] also observed in other metal derivatives such as lithium,[27] zinc and titanium.[28] The allenyl form is the most stable[29] and there is a prominent tendency to the location of the metal atom at the allenyl carbon, a situation still more favoured by the presence of a triorganosilyl substituent.[30] However, according to the Curtin-Hammett principle,[31] it cannot be discarded a higher reactivity of the propargyl form of the Grignard reagent. In fact, it is necessary to consider both propargyl and allenyl forms but also attacks at the alpha and gamma carbons of the propargyl/allenyl system. In the case of nitrone **9** and the addition of the unsubstituted Grignard reagent, the two preferred transition states *Re*-**TS-B1** and *Re*-**TS-C1**, both corresponding to the attack by the less hindered face (Figure 2), are competitive. When considering all the possible transition structures and the corresponding Boltzmann distribution derived from energy values, (see Supporting Information) it was predicted a 2.7:1 propargyl:allenyl ratio and a complete *trans*-

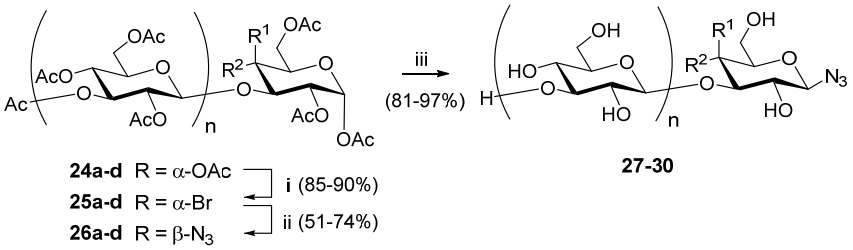
diastereoselectivity for both propargyl **11** and allenyl **12** derivatives, in good agreement with experimental results. On the other hand, for the addition of trimethylsilyl substituted Grignard reagent although the propargyl:allenyl ratio is correctly predicted to be 32:1, the lack of diastereoselectivity observed experimentally is not anticipated.

The copper-catalyzed alkyne-azide cycloaddition (CuAAC) in which final alkynes will be employed does not require protection of the hydroxyl and amino groups so, we prepared unprotected alkynyl pyrrolidines through reduction of the hydroxylamine moiety with Zn/HCl and further desilylation of the triple bond (Scheme 2). Under these conditions compound **17** was obtained from **8**. In this particular case, debenzylation would require hydrogenolytic conditions so, it should be carried out after condensation with the corresponding azide in order to keep the integrity of the triple bond. For hydroxylamine **9** a one-pot procedure including further deprotection of the hydroxyl group afforded hydrochloride **19**. The 1:1 mixture of hydroxylamines **18** was also treated with Zn/HCl affording a mixture of amines **21a** and **21b** which could be separated by flash chromatography, Further desilylation of **21** gave rise to compounds **22** in good chemical yields. In the case of hydroxylamines **10** and **20** the initial acidic treatment led to partial deprotection of the acetonide moiety so, complete deprotection was achieved in a one-pot procedure affording compounds **15** and **23**.



Scheme 5. Synthesis of alkynyl pyrrolidines. Reagents and conditions: (i) Zn, 1N HCl-dioxane (1:1), rt, 16 h. (ii) TBAF 1M in THF, rt, 7 h. (iii) TFA, rt, 12 h. (iv) 1N HCl, rt, 16 h.

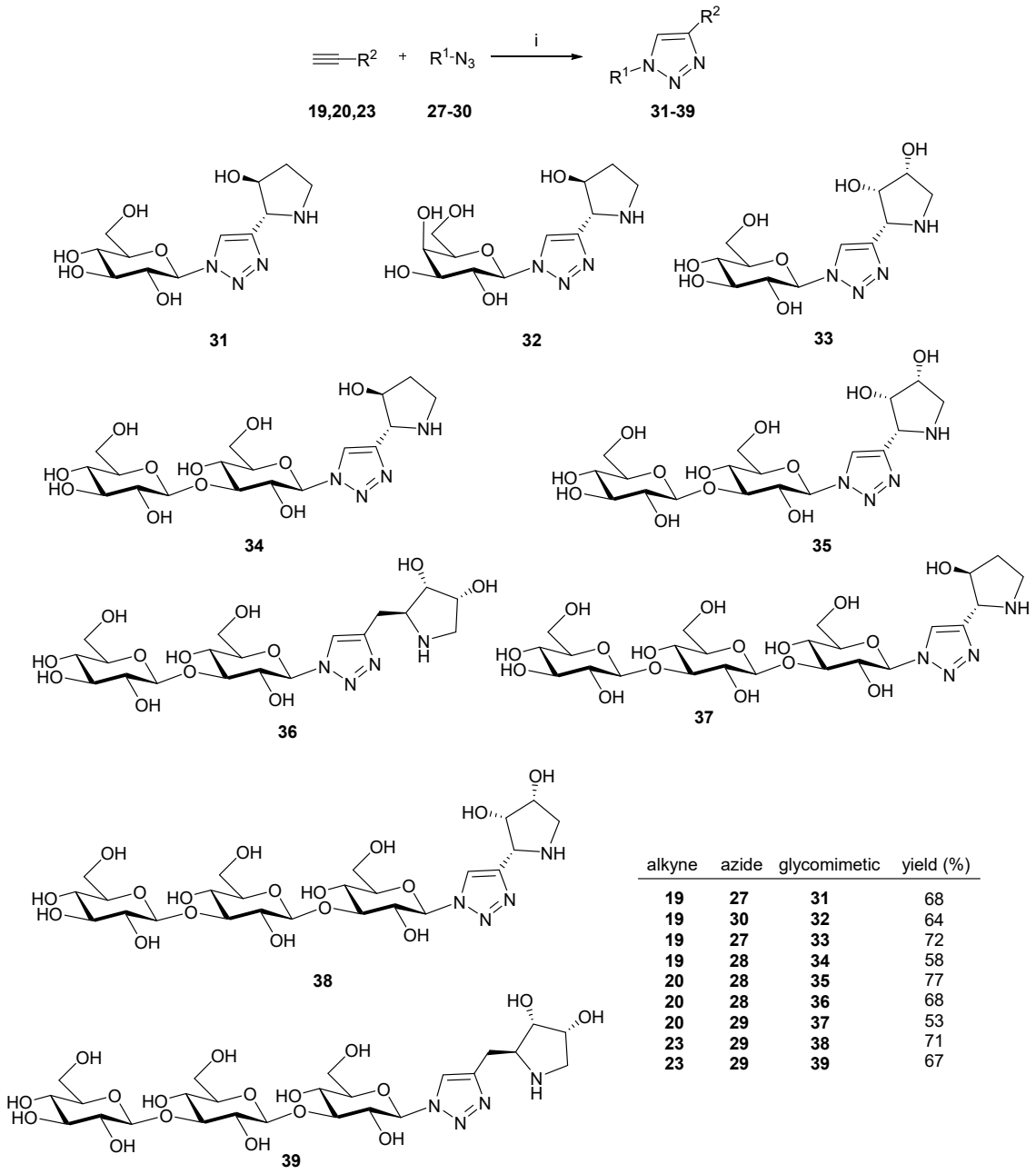
In general terms, the synthesis of alkynyl pyrrolidines **17, 19, 20, 22** and **23** is experimentally simple, with several one-pot processes and it takes place with good chemical yields thus rendering that sort of building blocks for click-chemistry very accessible. Next, we prepared glycosyl azides **27**-**30** derived from D-glucose, D-galactose and β-(1,3)-D-gluco di- and trisaccharides. Compounds **24**-**27** were synthesized from the corresponding peracetylated sugars **24**,[32] by formation of glycosyl bromides **25**, reaction with sodium azide in DMF as a solvent and further deprotection of the acetyl groups (Scheme 6).



n	R^1	R^2						
0	H	OAc	**25a**	(87%)	**26a**	(74%)	**27**	(96%)
1	H	OAc	**25b**	(89%)	**26b**	(63%)	**28**	(93%)
2	H	OAc	**25c**	(85%)	**26c**	(51%)	**29**	(81%)
0	OAc	H	**25d**	(90%)	**26d**	(52%)	**30**	(97%)

Scheme 6. Synthesis of glycosyl azides. Reagents and conditions: (i) HBr, AcOH. (ii), NaN_3, DMF. (iii) NaOMe, MeOH, rt, 1 h.

The CuAAC reaction was carried out under standard conditions[8a] by mixing 1M aqueous solutions of azide and alkyne with a 0.2 M solution of copper(II) acetate and adding 1:1 MeOH-H_2O and an excess of copper. After stirring at ambient temperature for 24 h target glycomimetics **31-39** were obtained in good yields (Scheme 7) and purified by ion-exchange chromatography.



alkyne	azide	glycomimetic	yield (%)
19	**27**	**31**	68
19	**30**	**32**	64
19	**27**	**33**	72
19	**28**	**34**	58
20	**28**	**35**	77
20	**28**	**36**	68
20	**29**	**37**	53
23	**29**	**38**	71
23	**29**	**39**	67

Scheme 7. Synthesis of glycomimetics. Reagents and conditions: (i) $Cu(OAc)_2$, Cu, sodium ascorbate, 1:1 MeOH-H_2O, 24 h, rt

Conclusions

In summary, a process for preparing pyrrolidinyl building blocks ready for CuAAC click-chemistry is reported. Installation of a triple bond in a pyrrolidine ring can be done by means of ethynylation and propargylation reactions. Ethynylation reaction proceeded with excellent results on both chemical yield and diastereoselectivity. For propargylation reaction it was necessary to prepare the Grignard derivative from

trimethylsilyl propargyl bromide; otherwise the allene derivative is the predominant product of the reaction. The different behaviour observed in the nucleophilic additions to cyclic nitrones is explained by DFT calculations within the margin of experimental error. The reaction of the synthesized alkynyl pyrrolidines with glycosyl azides afforded the corresponding glycomimetics in good overall yield. Application of this protocol to other glycomimetics and studies to fully delineate the stereoselectivity of propargylation reactions are currently under investigation in our laboratory.

Experimental Part

The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots was detected with 254 nm UV light or by spraying with 5% ethanolic phosphomolybdic acid. Column chromatography was carried out in a Buchi 800 MPLC system using silica gel 60 microns. Melting points were uncorrected. 1H and 13C NMR spectra were recorded on Bruker Avance 400 instrument in the stated solvent. Chemical shifts are reported in ppm (δ) relative to CHCl3 (δH = 7.26, δC = 77.0) in CDCl3. Optical rotations were taken on a JAS-CO P-1020 DIP-370 polarimeter. Elemental analyses were performed on a Perkin Elmer 240B microanalyzer or with a Perkin-Elmer 2400 instrument.

Trimethylsilylethynylation of Cyclic Nitrones. General Procedure A.

Propargylation of Cyclic Nitrones. General Procedure B.

Trimethylsilylpropargylation of Cyclic Nitrones. General Procedure C.

Reduction with Zn in acetic acid. General Procedure D.

Desilylation of trimethylsilylalkynes. General Procedure E.

Hydrolysis of acetonides. General Procedure F.

Synthesis of Glycosyl bromides. General Procedure G.

Azidation of Glycosyl Bromides. General Procedure H.

Deacetylation of Glycosyl azides. Procedure I

Copper-catalyzed Alkyne Azide Cycloaddition. General Procedure J.

(2*R*,3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-((trimethylsilyl)ethynyl)pyrrolidin-1-ol 8

Procedure A. (mg, 86 %). oil. $[\alpha]_D^{25}$ (, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1. Anal Calcd for $C_{31}H_{37}NO_4Si$: C, 72.20; H, 7.23; N, 2.72. Found: C, 72.58; H, 7.17 N, 2.91.

(2*R*,3*S*)-3-(tert-butoxy)-2-((trimethylsilyl)ethynyl)pyrrolidin-1-ol 9

Procedure A. (mg, 88 %). oil. $[\alpha]_D^{25}$ (, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1. Anal Calcd for $C_{13}H_{25}NO_2Si$: C, 61.13; H, 9.87; N, 5.48. Found: C, 61.05; H, 9.78 N, 5.53.

(3a*S*,4*R*,6a)-2,2-dimethyl-4-((trimethylsilyl)ethynyl)tetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-ol 10

Procedure A. (mg, 90 %). oil. $[\alpha]_D^{25}$ (, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1. Anal Calcd for $C_{12}H_{21}NO_3Si$: C, 56.44; H, 8.29; N, 5.48. Found: C, 56.38; H, 8.41 N, 5.31.

(2*R*,3*S*)-3-(*tert*-butoxy)-2-(prop-2-yn-1-yl)pyrrolidin-1-ol 11

Procedure B. (mg, 64 %). oil. $[\alpha]_D^{25}$ (, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1. Anal Calcd for $C_{11}H_{19}NO_2Si$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.11; H, 9.85 N, 6.96

(2*R*,3*S*)-3-(*tert*-butoxy)-2-(2λ^5-propa-1,2-dien-1-yl)pyrrolidin-1-ol 12

Procedure B. (mg, 33 %). oil. $[\alpha]_D^{25}$ (, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1. Anal Calcd for $C_{11}H_{19}NO_2Si$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.82; H, 9.50 N, 6.94.

(3a*S*,4*R*,6a*R*)-2,2-dimethyl-4-(3-(trimethylsilyl)prop-2-yn-1-yl)tetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-ol 15

Procedure C. (mg, 92%). oil. $[\alpha]_D^{25}$ (, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1. Anal Calcd for $C_{13}H_{23}NO_3Si$: C, 57.96; H, 8.61; N, 5.20. Found: C, 57.88; H, 8.53 N, 5.18.

16

Procedure D. (mg, 80%). oil.

17

Procedure E. (mg, 94%). oil.

18

Procedure D. (mg, 85%). oil.

19

Procedure E, then XXXXXXXXX. (mg, 76%). oil.

20

Procedure D, then procedure E, then procedure F. (mg, 72%). oil.

21a and 21b

Procedure D.

21a: (mg, 39%). oil.

21b: (mg, 39%).oil

22a

Procedure E. (mg, 93%). oil.

22b

Procedure E. (mg, 94%). oil.

23

Procedure D, then procedure E, then procedure F. (mg, 54%). oil.

25a

Procedure G. (mg, 85%). oil.

25b

Procedure G. (mg, 87%). oil.

25c

Procedure G. (mg, 85%). oil.

25d

Procedure G. (mg, 90%). oil.

26a

Procedure H. (mg, 74%). oil.

26b

Procedure H. (mg, 63%). oil.

26c

Procedure H. (mg, 51%). oil.

26d

Procedure H. (mg, 52%). oil.

27a

Procedure I. (mg, 96%). oil.

27b

Procedure I. (mg, 93%). oil.

27c

Procedure I. (mg, 81%). oil.

27d

Procedure I. (mg, 97%). oil.

31

Procedure J. (mg, 68%). oil.

32

Procedure J. (mg, 64%). oil.

33

Procedure J. (mg, 72%). oil.

34

Procedure J. (mg, 58%). oil.

35

Procedure J. (mg, 77%). oil.

36

Procedure J. (mg, 68%). oil.

37

Procedure J. (mg, 53%). oil.

38

Procedure J. (mg, 71%). oil.

39

Procedure J. (mg, 67%). oil.

Acknowledgments

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